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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/771,503	01/26/2001	Henry Yue	PC-0027 US	6227

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LEGAL DEPARTMENT
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	9

DATE MAILED: 04/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applic
09/771,503	Yue et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____ .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above, claim(s) *14-21* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-13* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Acknowledgment is made of applicants election with traverse of Group I drawn to the isolated cDNA encoding SEQ ID NO:2. The traversal is on the ground that the restriction is not necessary as it would not be an undue burden to search Groups II, III and IV in addition to elected Group I. This has been considered and found partially persuasive. Group II will be joined to Group I for examination at this time.

2. Claims 1-21 are pending. Claims 14-21, drawn to non-elected inventions, are withdrawn from consideration. Claims 1-13 are examined on the merits. The examination of claims 12 and 13 will not be limited to polynucleotide-polynucleotide binding as stated in the Restriction Requirement of Paper No. 7.

Information Disclosure Statement

3. The references submitted with the IDS filed March 20, 2001 have been considered. The PTO-1449 form listing these references was not included in the filing, therefore the examiner cannot make of record the submitted references. Applicant is invited to supply the required PTO-1449 form in response to this office action.

Claim Rejections - 35 USC § 101 and 112

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claim rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a asserted utility or a well established utility.

Claims 1-6 are drawn to the polynucleotides comprising nucleic acid sequences encoding SEQ ID NO:1, the polynucleotides comprising SEQ ID NO:2, compositions, vectors and host cells thereof. Claim 7 is drawn to a method of producing a recombinant protein comprising the

expression of the polynucleotide of claim 1. Claims 8-11 are drawn to a method of using a cDNA to detect expression of a nucleic acid in a sample comprising the detection of hybridization complexes and the comparison of the detected hybridization complexes to the hybridization complexes in a standard sample. The specification asserts that these polynucleotides are useful in the detection of colon disorders such as cancer and polyps. The specification states on page 10, lines 16-18, that the majority of patients having colon disorders comprising cancer or polyps showed downregulation of this gene (Table 1) and that this downregulation is consistent with genes whose differential expression is associated with colon cancer (page 10, lines 16-18). However, an examination of Table 1 finds the experimental data does not support this allegation. The data for the differential expression is put forth as the log base 2 value of the Cy5 to Cy3 ratio. Page 6, lines 19-21 states that Column 3 lists the diseased samples labeled with Cy5 and that column 4 lists the corresponding normal samples labeled with Cy3. If the expression of the gene is lower colon cancer and polyps versus normal tissues the ratio of Cy5 to Cy3 should be less than one in cases of colon cancer or polyps. A value of 1 would be zero in the log base 2 scale, and values of less than one would be negative number in the log base 2 scale. Examination of the log base 2 values shows numbers ranging from -3.64, -3.12, -1.92, +0.14, +0.52, +1.04 for polyps and numbers ranging from -3.06, -2.73, -0.53, -2.86, -2.18, -1.99, -0.54, +1.1 and +1.29 for colon tumors. This data indicates that tumor tissue and polyp tissue do not exhibit a decrease in the gene expression of ITL, as they include positive numbers indicating a ratio of Cy5/Cy3 of greater than one. Conversion of the values in Column 1 to base 10 by using the log base 2 value as a power of 2 results in values of 0.081, 0.115, 0.264, 1.10, 1.43, 2.05 for polyps and values of 0.119, 0.151, 0.678, .0.137, 0.220, 0.251, 0.687, 2.14, and 2.44 for tumors, which again does not provide support for the diagnosis of colon disorders comprising cancer or polyps by means of determining the relative expression of polynucleotides encoding SEQ ID NO:1. The examiner does not find an adequate nexus between the asserted properties of the claimed polynucleotides and the evidence of record.

Claim 2 is drawn in part to the polynucleotides of SEQ ID NO:6 and 7. The specification describes these as mammalian variants of SEQ ID NO:2 obtained through a homology search in

the ZOOSEQ database (page 11, lines 9-12). The examiner contends that SEQ ID NO:6 is from rat as its identity was disclosed as RATRNOT04 (page 11, line 11). The species from which SEQ ID NO:7 was derived is not disclosed in the specification. The specification asserts that SEQ ID NO:6 and 7 are particularly useful for producing transgenic cell lines or organisms. The specification asserts (page 23, lines 11-13) that expression of the transgene can be monitored by analysis of phenotype, tissue-specific mRNA expression, or serum and tissue protein levels in transgenic animals before, during and after challenge with experimental drug therapies. However, for the reasons set forth in the paragraph above, the specification does not provide objective evidence that a nexus exists between the lack of expression of the nucleic acids encoding SEQ ID NO:1 and the presence of colon tumors or polyps and therefore the specification does not provide a nexus between the loss of expression of SEQ ID NO:6 or SEQ ID NO:7 and colon tumors or polyps in the rat. The specification provides no objective evidence that restoration of expression of SEQ ID NO:2, 6 or 7 in tumor tissue or polyp tissue can induce a normal phenotype in said tissues. Therefore, even if the specification provided support for the loss of expression of SEQ ID NO:1 in colon tumors, it cannot be assumed that the restoration of expression of the claimed polynucleotides, after drugs or other agents were administered to or contacted with transgenic animal or cell lines expressing SEQ ID NO:6 or 7, would be indicative of a therapeutic response. The specification does not teach that the loss of expression of SEQ ID NO:1 is a cause of the malignant phenotype versus an effect of malignancy, therefore, on cannot infer that the re-establishment of SEQ ID NO:1 would reverse the cancerous phenotype. Cancer is a complex and multiple step process that proceeds by the acquisition of successive genetic insults (A. Hagemeijer, Leukemia, 1992, Vol. 6, Suppl. 4, pp. 16-18) resulting in accumulation of mutant forms of proteins and disruption of growth control (H. Varmus, Oncogenes and the Molecular Origins of Cancer, Weinburg ed., 1989, p. 36, last paragraph). Thus the malignant phenotype is subject to variables beyond the loss of expression of a single protein such as ITL. Therefore without objective evidence in the specification, one of skill in the art cannot assume that polynucleotides or drugs which increase the expression of ITL would function by reversing the

malignant phenotype of tumor cells. Neither can it be assumed that decreasing or eliminating the expression of ITL in normal cells would render the cells tumorigenic.

Claims 12 and 13 are drawn to a method of using a cDNA to screen a plurality of molecules or compounds for binding to the cDNA comprising the polynucleotides which encode SEQ ID NO:1. Claim 13 specifically embodies molecules or compounds of DNA, RNA, peptide nucleic acids, artificial chromosome constructions, peptides, transcription factors, repressors and regulatory molecules. The method entails combining the cDNA comprising the nucleic acid encoding SEQ ID NO:1 or the complement of SEQ ID NO:1 with a plurality of molecules under conditions to allow specific binding, wherein the detection of a molecule which specifically binds to said cDNA is the object of the method. The specification asserts (page 10, lines 16-18) that loss of expression of SEQ ID NO:1 in samples is indicative of colon cancer. Thus, the specification alleges that the disclosed cDNA is useful for detecting specific binding to polynucleotides and the specification has disclosed that the complete complements of polynucleotides of SEQ ID NO:2, 3, 4 and 5 can be used to detect the polynucleotides which encode SEQ ID NO:1. However, the specification does not assert a specific, substantial credible utility for said peptides, transcription factor, repressors and regulatory molecules which bind to the polynucleotides encoding SEQ ID NO:1. The only function identified for said molecules is that they bind to the claimed polynucleotides. The specification does not teach the activation or inhibition of the peptides, transcription factor, repressors and regulatory molecules when bound to the claimed polynucleotides. Neither does it teach the activation or inhibition of the the claimed polynucleotides when bound to peptides, transcription factor, repressors and regulatory molecules. The specification does not teach the biological significant of a complex of the claimed polynucleotides with the peptides, transcription factor, repressors and regulatory molecules with respect to a specific pathological condition. The only function attributed to these generalized peptides, transcription factors, repressors and regulatory molecules is that they bind to the disclosed polynucleotides. This claimed subject matter is not supported by a specific, substantial and credible utility because the function of "binding" is generally applicable to a broad class of

subject matter. Much further work and characterization would be required to identify or reasonable confirm a "real world" use.

Given the conflict between the asserted utility and the data presented in Table 1, credibility of any utility cannot be assessed for the polynucleotides of SEQ ID NO:2 or the polynucleotides encoding SEQ ID NO:1. Due to the lack of an asserted specific, substantial credible utility for the peptides, transcription factors, repressors and regulatory molecules which putatively bind to the disclosed polynucleotides, credibility of any utility cannot be assessed for said peptides, transcription factors, repressors and regulatory molecules. Because of the lack of a specific, substantial credible utility for the non-human homologs encoding ITL, credibility of any utility cannot be assessed for SEQ ID NO:6 and SEQ ID NO:7. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids, peptides, transcription factors, repressors and regulatory molecules which putatively bind to the disclosed polynucleotides.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

8. In the event that applicant would overcome the rejection under 36 U.S.C. 101, above, the following rejections will apply.

9. Claim 7 would be rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 7 is drawn to a method of using a host cell comprising a vector comprising a nucleic acid sequence encoding a protein having the amino acid sequence of SEQ ID NO:1 to produce a protein. The specification teaches SEQ ID NO:1 to be ITL, related to mouse ITL found in the paneth cells of the mouse ileum. Komiya et al (Biochemical and Biophysical Research Communications, 1998, Vol. 251, pp. 759-762, of the IDS filed 3/20/01) discloses that attempts to produce mouse ITL by recombinant expression of cDNA in both prokaryotic and eukaryotic systems failed due to a dramatic reduction in growth rate and no expressed protein was detected. Komiya et al teaches that this correlates with the fact that Paneth cells are involved in defense against microorganisms, and the expressed ITL is toxic.

The instant specification does not teach a method of producing a recombinant protein which would overcome this problem of toxicity to the host cell and result in the isolation of recombinant SEQ ID NO:1. Due to due to this unreliability in the art and the lack of teachings in the specification that address this problem, one of skill in the art would be subject to undue experimentation in order to practice the claimed invention.

10. Claim 2, 12 and 13 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A)Claim 2 is drawn in part to an isolated cDNA comprising SEQ ID NO:4 and SEQ ID NO:5. Both SEQ ID NO:4 and 5 contain numerous "N" residues indicative of an undefined nucleotide residue. The specification does not teach that substitution of all of G, C, A and T in place of the "N" residues would result in polynucleotides which would have the same use as the ITL polynucleotides of SEQ ID NO:1, nor does the specification teach a use for variant polynucleotides which would not function as claimed.

In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that

while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that an adequate written description of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention..

As such, the polynucleotide sequences of SEQ ID NO: 4 and 5 have only been partially defined. This is insufficient to support the claim as provided by the Revised Interim Written Description Guidelines published in the January 5, 2001 Federal Register at Volume 66, Number 4, pages 1099-1111.

(B)Claims 12 and 13 are drawn to a method of using a cDNA to screen a plurality of molecules or compounds for binding to the cDNA comprising the polynucleotides which encode SEQ ID NO:1. Claim 13 specifically embodies molecules or compounds of DNA, RNA, peptide nucleic acids, artificial chromosome constructions, peptides, transcription factors, repressors and regulatory molecules. The method entails combining the cDNA comprising the nucleic acid encoding SEQ ID NO:1 or the complement of SEQ ID NO:1 with a plurality of molecules under conditions to allow specific binding, wherein the detection of a molecule which specifically binds to said cDNA is the object of the method. The specification asserts (page 10, lines 16-18) that loss of expression of SEQ ID NO:1 in samples is indicative of colon cancer. Thus, the specification teaches that the disclosed cDNA is useful for detecting specific binding to polynucleotides and the specification has disclosed that the complete complements of polynucleotides of SEQ ID NO:2, 3, 4 and 5 can be used to detect the polynucleotides which encode SEQ ID NO:1. However, the specification has not provided a written description of the structure of specific peptides, transcription factors, repressors and regulatory molecules that bind to the cDNA of the instant invention and binding to the polynucleotides encoding SEQ ID NO:1 is the only functional activity identified with the undisclosed peptides, transcription factors, repressors and regulatory molecules. As stated in the paragraph supra, a description of a genus by functional activity only does not provide an adequate written description of the genus.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8(d) recites: "comparing hybridization complex formation with a standard, wherein the comparison indicates expression of the cDNA in the sample". Firstly, the method objective as stated in the preamble is to detect expression of a nucleic acid in a sample, not to detect expression of the cDNA in the sample. Furthermore, a comparison results in the observation of a difference between the sample and the standard. The claim, however, does not incorporate the difference between the sample and the standard into the final method step, and therefore is indefinite. As such, the practice of claim 8 would indicate the expression SEQ ID NO:1 in every possible sample as there is no method step relating the outcome of the comparison with the expression of a nucleic acid. For purpose of examination, the claim 8(d) will be read as --comparing hybridization complex formation with a standard, wherein detection of a higher level of hybridization complex in the sample is indicative of expression of the nucleic acid.--

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

14. Claim 2(c) is rejected under 35 U.S.C. 102(e) as being anticipated by Seilhammer et al (09/540,212). Claim 2(c) is drawn in part to the polynucleotide of SEQ ID NO:6. Seihammer et al discloses the polynucleotide of SEQ ID NO:65953 which is identical to that claimed.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Double Patenting

15. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

16. Claim 2, part (c) is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1 of copending Application No. 09/540,212. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

17. Claim 2(b) is directed to the same invention as that of claim 1 of commonly assigned 09/540,212. The issue of priority under 35 U.S.C. 102(g) and possibly 35 U.S.C. 102(f) of this single invention must be resolved.

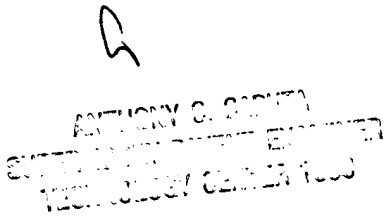
Since the Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302), the

assignee is required to state which entity is the prior inventor of the conflicting subject matter. A terminal disclaimer has no effect in this situation since the basis for refusing more than one patent is priority of invention under 35 U.S.C. 102(f) or (g) and not an extension of monopoly.

Failure to comply with this requirement will result in a holding of abandonment of this application.

Conclusion

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



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Patent Examiner, Group 1642
April 5, 2002